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Objective assessment of cervical stiffness after administration of misoprostol for intrauterine contraceptive insertion

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Abstract: **PURPOSE** The goal of this study was to objectively quantify cervical stiffness in misoprostol users prior to IUC insertion and at follow-up consultation to evaluate the feasibility of assessing cervical stiffness and to study the influence of misoprostol on cervical softening. **MATERIALS AND METHODS** This was a cross-sectional study that evaluated 40 women who wished to use the LNG IUS. These women were evaluated immediately before LNG IUS insertion and 6 weeks later at follow-up consultation. Participants received 200 g of misoprostol combined with 75 mg of diclofenac in a single tablet orally (Arthrotec forte 75/200®), Pfizer, USA) 6-12 h prior to insertion in "off label" use. On both occasions, cervical stiffness was determined using a novel medical device based on the aspiration technique. The Wilcoxon rank-sum and the Wilcoxon signed-rank test were applied to compare cervical stiffness assessments at insertion of the IUD and at follow-up. **RESULTS** For the first time, cervical stiffness was quantitatively assessed in misoprostol users prior to IUD insertion, proving that the aspiration technique enables detection of pharmacologically induced cervical changes, and also that misoprostol has a detectable softening effect on cervical tissue. **CONCLUSION** The clinical value of the detected cervical softening after misoprostol administration remains unclear. Aspiration measurements could be helpful in searching for the ideal candidate, the appropriate route, dosage and interval of misoprostol intake prior to IUC insertion.

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Objective assessment of cervical stiffness after administration of misoprostol for intrauterine contraceptive insertion

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Abstract

Purpose:

This study aims at the objective quantification of cervical stiffness in misoprostol users prior to IUC insertion and at follow up consultation to evaluate the feasibility of assessing cervical stiffness and to study the influence of misoprostol on cervical softening.

Materials and Methods: This was a cross-sectional study that evaluated 40 women who wished to use the LNG IUS. These women were evaluated immediately before LNG IUS insertion and 6 weeks later at follow up consultation. Participants received 200 µg of misoprostol combined with 75 mg of diclofenac in a single tablet orally (Arthrotec forte 75/200®, Pfizer, USA) 6 to 12 hours prior to insertion in “off label” use. On both occasions, cervical stiffness was determined using a novel medical device based on the aspiration technique. The Wilcoxon rank-sum and the Wilcoxon signed-rank test were applied to compare cervical stiffness assessments at insertion of the IUD and at follow up.

Results: For the first time, cervical stiffness was quantitatively assessed in misoprostol users prior to IUD insertion, proving that the aspiration technique enables detection of pharmacologically induced cervical changes, and also that misoprostol has a detectable softening effect on cervical tissue.

Conclusion: The clinical value of the detected cervical softening after misoprostol administration remains unclear. Aspiration measurements could be helpful in searching for the ideal candidate, the appropriate route, dosage and interval of misoprostol intake prior to IUC insertion.

Introduction

Intrauterine contraceptives (IUC) belong to the most widely used family planning methods worldwide. Modern IUCs are reversible, long-acting, safe and cost-effective [1]. However, IUC uptake varies significantly across the world. Fear of pain during insertion is one of the well-known reasons that may prevent women from choosing an IUC as their method of choice [2,3]. For the vast majority, IUC insertion does not cause severe pain, but around 10 % of (multi-)para (P) [4] and 20 % of nulli-para (0P) [5] women report this procedure as very painful. It may, therefore, seem surprising that the need for pain relief during IUC insertion is still under debate and no generally accepted concept exists.

Application of misoprostol, a prostaglandin analogue, activates inflammatory reactions [6,7] and induces microstructural changes in the cervical tissue leading to a disorganization of the collagenous network and thus cervical tissue softening (sometimes also called cervical ripening) [8,9].

In OB/GYN, misoprostol has been widely administered in “off-label” usage to initiate the expected cervical softening as part of easing cervical dilation [4,10,11]. However, the cervical softening which is an indirect clinical feature and a requisite to facilitate cervical manipulations has so far never been quantified in-vivo.

The never proven softening effect of misoprostol was also evaluated for pain reduction in IUC insertion [3], especially exploring the possible advantage for 0P, who generally present a narrow, stiff and un-stretched cervix [10,12,13]. Indeed, some studies found the use of misoprostol leads to an easier IUC passage through the cervical canal [14-16] and greater cervical dilation [15], but several other studies could not support the superiority of misoprostol administration, neither from the

doctor's judgment regarding ease of insertion [4,17,18] nor from the patient's judgment on lower pain perception [4,17]. In a large review, Gemzell-Danielsson *et al.* [19] found no conclusive evidence that prophylactic pharmacological interventions reduce pain on IUC insertion. This conflicting data, doubting the effectiveness of misoprostol, might arise from a lack of a standardized protocol for IUC insertion and drug application (route, time dosage) [19-22]. However, despite the lack of clear evidence of a beneficial effect of misoprostol, health care providers frequently recommend misoprostol administration in the belief that pain during IUC insertion is reduced [23].

The state of scientific knowledge regarding the efficacy of different misoprostol regimen on cervical softening and on IUC insertion in general needs further research. The quantitative and objective assessment of cervical softening using a dedicated instrument is the first step towards an improved understanding. Such an instrument allows finding the optimal misoprostol treatment in terms of cervical softening which then can be further evaluated in terms of ease of insertion and its impact on pain management during IUC insertion.

In the present study, we focused on acquiring objective data to measure the cervical stiffness using the aspiration method (ASP) [24]. Recently, the aspiration method has been tested successfully in a clinical study to describe cervical stiffness on 50 non-pregnant and 50 pregnant subjects. For the first time the in-vivo measurements allowed us to quantify the continuous cervical softening during pregnancy [24,25]. To the best of our knowledge, aspiration is the only available and reliable method that allows us to objectively quantify the stiffness of the cervical tissue on humans in-vivo.

This study aims at the objective quantification of cervical stiffness in misoprostol users prior to IUC insertion and at follow up consultation to evaluate the feasibility of

assessing cervical stiffness and to study the influence of misoprostol on cervical softening.

Method

Ethical approval

This cross-sectional study was approved by the IRB (KEK Zurich StV02/2007 and later amendments) and was conducted according to the Declaration of Helsinki. Subject informed consent was prerequisite for the study involvement.

Participant selection

From July 2013 all women presenting for IUC placement at our private office were invited to take part in the study. We focused on the 52 mg LNG IUS (LNG IUS, Mirena®, Bayer Healthcare, Germany), since in this unit more than 90% of the women chose an LNG IUS as their IUC. Non-inclusion criteria were communication problems, prior surgery on the cervix, untreated premalignant or malignant changes on the cervix, contraindications to using a LNG IUS, and the use of misoprostol or non-steroidal anti-inflammatory drugs. By October 2014, 40 women were included.

Misoprostol and Diclofenac administration

Participants received 200 µg of misoprostol combined with 75 mg of diclofenac in a single tablet orally (Arthrotec forte 75/200®, Pfizer, USA) 6 to 12 hours before insertion in “off label” use.

Aspiration measurement

Directly before LNG IUS insertion, aspiration measurements (Fig. 1) were performed, as previously described in detail [24,25] to measure cervical stiffness. To this end, the aspiration tube is placed orthogonally on the ecto-cervix at the 12 o'clock

position. Negative pressure (limited at maximum 500 mbar) on the cervical epithelium is applied to elevate the underlying tissue to a predefined level of deformation (4 mm). The required pressure to deform the tissue (closure pressure: p_{cl}) is registered. It is proportional to the stiffness of the cervical stroma [24,25] .

Follow Up

Aspiration measurements were repeated at regular follow up consultations including a sonographic IUC position check around 6 weeks after insertion.

Study population

40 Caucasians aged from 22 to 49 years of age (mean: 35 years), mostly parous subjects. 25 subjects underwent a first LNG IUS insertion, 15 subjects had a LNG IUS replacement.

Statistics

Statistical analysis was performed with the statistical computing environment R: A Language and Environment for Statistical Computing, Open Source Software, 2012. The Wilcoxon rank-sum test was used to compare differences between the previously investigated control group [24] and the two groups in this study, both prior to IUC placement (first insertion and replacement) and at follow up. For comparison of values of the same subjects at insertion and at follow up, the Wilcoxon signed-rank test was applied.

Results

Insertion:

All new LNG IUS insertions as well as all replacements could be executed successfully. Immediate transvaginal ultrasound position check confirmed correct positioning in all cases, no perforation occurred.

Aspiration measurements:

Cervical stiffness (p_{cl}) was successfully assessed in all subjects. The primary outcome was the p_{cl} value (i.e. cervical stiffness) at insertion after misoprostol intake and at follow up without misoprostol. We found average values for p_{cl} of 290 mbar \pm 138 mbar (mean \pm SD) at insertion and 324 \pm 138 mbar at follow up showing no significant difference when assessing the group as a whole. However, when we divided the study population into first LNG IUS insertion and LNG IUS replacement, we found 230 mbar \pm 93 mbar (mean \pm SD) in the first LNG IUS insertion group ($n = 25$), and p_{cl} of 396 mbar \pm 90 mbar in the LNG IUS replacement group ($n = 15$). The comparison with a historical control subjects ($n = 50$) published in Badir et al. [25] (320 mbar \pm 120 mbar) revealed that p_{cl} at insertion was significantly lower ($p = 0.005$) in the first LNG IUS insertions indicating a reduction in cervical stiffness. In contrast, the comparison between control subjects and LNG IUS replacement demonstrated a higher p_{cl} in this group, but did not reach a statistical significance ($p = 0.08$). Additionally, comparison of p_{cl} values at insertion between first insertions and replacements showed a significant difference ($p \leq 0.001$). Pre and post-comparison of p_{cl} at insertion and at follow up demonstrated a differentiated behavior in cervical stiffness change in the two groups. In the first LNG IUS insertion group, cervical stiffness increased significantly ($p \leq 0.001$) to a similar level (308 mbar \pm 105) at follow up as that expected from control group (320 mbar \pm 120 mbar) while in the LNG IUS replacement group cervical stiffness decreased significantly to the level of the control group ($p = 0.03$). See Fig. 2 for mean and standard deviation values, and

Fig. 3 for subject specific data. Closure pressure values obtained at follow up are not statistically different from the control group (first insertion, $p = 0.6$ and consecutive insertion, $p = 0.7$). The same non-significant finding is revealed in the comparison between p_{cl} values between follow up after first LNG IUS placement and LNG IUS replacement ($p = 0.5$).

Discussion

For the first time, cervical stiffness was quantitatively assessed in misoprostol users prior to LNG IUS insertion, showing that i) ASP is able to detect pharmacologically induced cervical changes, and ii) misoprostol has a detectable softening effect on cervical tissue at first insertion.

We compared measurements taken from women at their first LNG IUS insertion with their measurements taken around 6 weeks later (when there were no effects from the previous misoprostol administration). It was found that cervical stiffness was significantly lower initially with misoprostol but after 6 weeks cervical stiffness recovered to the reference stiffness values of non-pregnant women.

In contrast, the group with an LNG IUS replacement did not show a decrease of cervical softening caused by misoprostol. Cervical stiffness was not significantly different, at insertion and at follow up some weeks later, and was comparable to the reference cohort. These results are in line with Heikinheimo *et al.*, [4]. In their study misoprostol did not have an effect on the ease of insertion in subjects having a LNG IUS replacement.

This surprise finding demands a further explanation. We can only assume that prostaglandin (misoprostol) induced cervical softening was blocked in the LNG IUS exchangers by the locally released LNG. This assumption is supported by the recent

literature. Murine infection-induced preterm birth models provided insight into the molecular and microstructural processes leading to cervical softening. Prostaglandins were found to be the promoter of these remodeling processes. Increased GAG synthesis induced by prostaglandins led to disintegration of the collagenous network thus leading to a detectable cervical softening. In these cases the softness of the cervical tissue was indistinguishable from that of cervixes at term. Moreover using the same murine model, it was demonstrated that administration of progesterone inhibited prostaglandin induced cervical softening [6].

In our study, 200 µg misoprostol and 75 mg diclofenac was given orally 6 - 12 hours prior to insertion of the LNG IUS. The oral administration route was chosen for practical reasons combined with a smaller dose of misoprostol, as discussed by Sääv *et al.* [14], to lower the incidence of uterine cramps. Nonetheless, diclofenac was co-administered, as suggested by Gemzell-Danielsson *et al.* [19], to manage prostaglandin-induced side effects. In previous IUC insertion studies misoprostol was administered buccally [10], sublingually [14] or vaginally [15]. In contrast to our protocol the dosage of 400 µg administered in the above mentioned studies was significantly higher and the time lag between misoprostol intake and insertion was within 1 to 4 hours significantly shorter [4,10,17]. We decided for a longer priming interval based on the recommendations of different authors [11,14,21,22] critically addressed the importance of the time interval to induce significant cervical softening and to obtain the benefit of misoprostol for insertion. Since we measured a significant softening after misoprostol intake in the first LNG IUS insertions, our observation supports the importance of a priming interval of 6 to 12 hours. However, this study was not designed to answer this question.

The exact role of diclofenac remains unclear, but we believe that the very low rate of misoprostol induced uterine cramps (5%) in this study is the result of the diclofenac effect, as assumed in Bahamondes *et al.* [22].

A limitation of this study is the lack of sub-analysis of the misoprostol effect on OP versus P due to the small number of OP subjects, and the restriction to only one typically used IUC. Another possible limitation to this study is that it was not conducted as a blind randomized controlled trial and cervical softening is an indirect clinical feature that does not allow to judge e.g. about ease of insertion, extent of cervical dilation or pain during IUC insertion.

In summary, the aspiration method allowed simple and quantitative cervical stiffness assessment to evaluate the softening effect of misoprostol on the cervical tissue. Our results are indicative for misoprostol induced softening in subjects for first LNG IUS insertion. As a preliminary clinical consequence, based on our results, we could suggest a differentiated misoprostol administration policy, i.e. women undergoing first LNG IUS insertion might benefit from 200 µg oral misoprostol administration 6 - 12 hours prior to insertion (evidence of cervical softening), whilst women undergoing LNG IUS replacement might not benefit from it (lack of cervical softening). However, cervical softening is an indirect clinical value and should be further studied by assessing clinical features such as ease of insertion or pain during insertion. Further aspiration measurements could be helpful in searching for the ideal candidate, the appropriate route, dosage and interval of misoprostol intake prior to IUC insertion.

References

- 1 Winner B, Peipert J, Qiuhong Z, Buckel C, Madden T et al. Effectiveness of Long-Acting Reversible Contraception. N Engl J Med 2012; 366: 1998–2007.

- 2 Hubacher D, Reyes V, Lillo S, Zepeda A, Chen P et al. Pain from copper intrauterine device insertion: randomized trial of prophylactic ibuprofen. *Am J Obstet Gynecol* 2006; 195: 1272–7.
- 3 Allen R, Bartz D, Da G, Hubacher D, Brien OP. Interventions for pain with intrauterine device insertion. *Cochrane Database Syst Rev* 2009.
- 4 Heikinheimo O, Inki P, Kunz M, Parmhed S, Anttila A-M et al. Double-blind, randomized, placebo-controlled study on the effect of misoprostol on ease of consecutive insertion of the levonorgestrel releasing intrauterine system. *Contraception* 2010; 81: 481–6.
- 5 Marions L, Lökvist L, Taube A, Johansson M, Dalvik H et al. Use of the levonorgestrel releasing-intrauterine system in nulliparous women - a noninterventional study in Sweden. *Eur J Contracept Reprod Health Care* 2011; 16: 126–34.
- 6 Gonzalez J, Franzke C, Yang F, Romero R, Girardi G. Complement activation triggers metalloproteinases release inducing cervical remodelling and preterm birth in mice. *Am J Pathol* 2011; 179: 838 - 848.
- 7 Norman M, Ekman G, Malmström A. Prostaglandin E2-induced ripening of the human cervix involves changes in proteoglycan metabolism. *Obstet Gynecol* 1993; 82: 1013–1020.
- 8 Akins M, Luby-Phelps K, Bank R, Mahendroo M. Cervical softening during pregnancy: regulated changes in collagen crosslinking and composition of extracellular proteins in the mouse. *Biol Reprod* 2011; 84: 1053-1062.
- 9 Myers KM, Feltovich H, Mazza E, Vink J, Bajka M et al. The mechanical role of the cervix in pregnancy 2015; 48: 1511-1523.
- 10 Lathrop E, Haddad L, McWhorter CP, Goedken P. Self-administration of misoprostol prior to intrauterine device insertion among nulliparous women: a randomized controlled trial. *Contraception* 2013; 88: 725–9.
- 11 Choksuchat C, Cheewadhanaraks S, Getpook C, Wootipoom V, Dhanavoravibul K. Misoprostol for cervical ripening in non-pregnant women: a randomized double-blind controlled trial of oral versus vaginal regimens. *Hum Reprod* 2006 ;21: 2167–2170.
- 12 Farmer M, Webb A. Intrauterine device insertion-related complications: can they be predicted? *J Fam Plann Reprod Health Care* 2003; 29: 227–231.
- 13 Kaislasuo J, Suhonen S, Gissler M, Lähteenmäki P, Heikinheimo O. Uterine perforation caused by intrauterine devices: clinical course and treatment. *Hum Reprod* 2012; 27: 2658–63.
- 14 Sääv I, Aronsson a, Marions L, Stephansson O, Gemzell-Danielsson K. Cervical priming with sublingual misoprostol prior to insertion of an intrauterine

- device in nulliparous women: a randomized controlled trial. *Hum Reprod* 2007; 22: 2647–2652.
- 15 Scavuzzi A, Souza ASR, Costa R, Amorim MMR. Misoprostol prior to inserting an intrauterine device in nulligravidas: a randomized clinical trial. *Hum Reprod* 2013; 28: 2118–2125.
 - 16 Lotke PS, Tiwari A, Nuño VL. Inserting intrauterine devices in nulliparous women : is misoprostol beneficial ? A registered clinical trial. 2013; 1: 62–68.
 - 17 Espey E, Singh RH, Leeman L, Ogburn T, Fowler K et al. Misoprostol for intrauterine device insertion in nulliparous women: a randomized controlled trial. *Am J Obstet Gynecol* 2014; 210: 1–5.
 - 18 Dijkhuizen K, Dekkers OM, Holleboom CG, Groot CJM, Hellebrekers BWJ, et al. Vaginal misoprostol prior to insertion of an intrauterine device: an RCT. *Hum Reprod* 2011; 26: 323–329.
 - 19 Gemzell-Danielsson K, Mansour D, Fiala C, Kaunitz M, Bahamondes L. Management of pain associated with the insertion of intrauterine contraceptives. *Hum Reprod Update* 2013; 19: 419–427.
 - 20 Li YT, Kuo TC, Kuan LC, Chu YC. Cervical softening with vaginal misoprostol before intrauterine device insertion. *Int J Gynaecol Obstet* 2005; 89: 67–68.
 - 21 Li Y-T, Wen-Ling L, Peng-Hui W. Difficult intrauterine device insertion. *Hum Reprod* 2011; 26: 2192–2193.
 - 22 Bahamondes L, Mansour D, Fiala C, Kaunitz AM, Gemzell-Danielsson K. Practical advice for avoidance of pain associated with insertion of intrauterine contraceptives. *J Fam Plann Reprod Health Care* 2014;40:54–60. [182] Crane J. prime the cervix for hysteroscopy ? *Obstet Gynecol Manag* 2008; 20: 27–29.
 - 23 Ward K, Jacobson JC, Turok DK, Murphy P. A survey of provider experience with misoprostol to facilitate intrauterine device insertion in nulliparous women. *Contraception* 2011; 84: 594–599.
 - 24 Badir S, Bajka M, Mazza E. A novel procedure for the mechanical characterization of the uterine cervix during pregnancy. *J Mech Behav Biomed Mater* 2013; 27: 143–153.
 - 25 Badir S, Mazza E, Zimmermann R, Bajka M. Cervical softening occurs early in pregnancy: characterization of cervical stiffness in 100 healthy women using the aspiration technique. *Prenat Diagn* 2013; 33: 737–741.

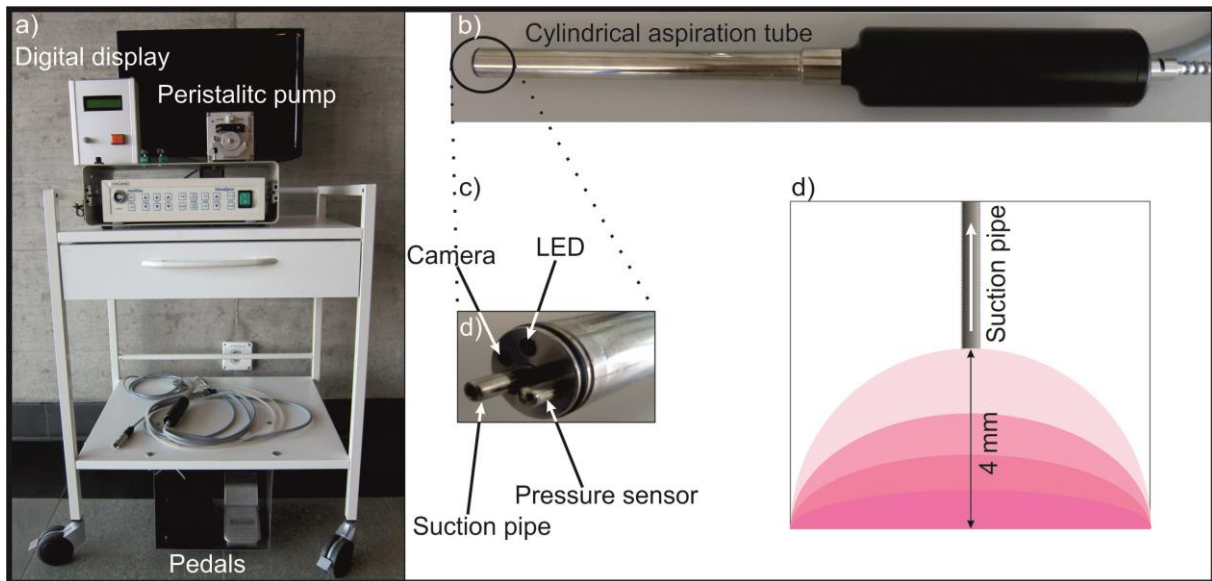


Fig. 1 Aspiration device and measurement principle: (a) Trolley with the peristaltic pump, aspiration tube, pedals, and other technical equipment; (b) view of the cylindrical aspiration tube with the round contact-opening (diameter of 8 mm) at the tip is placed at 12 o'clock position on the cervix.; (c) inside of the aspirator head; (d) The pressure in the tube is reduced by extraction of air through the suction pipe. Cervical tissue is deformed into the aspiration tube until the tissue vault reaches and closes the suction pipe. The corresponding value of negative pressure is called closing pressure (p_{cl}) and is the output of the measurement.

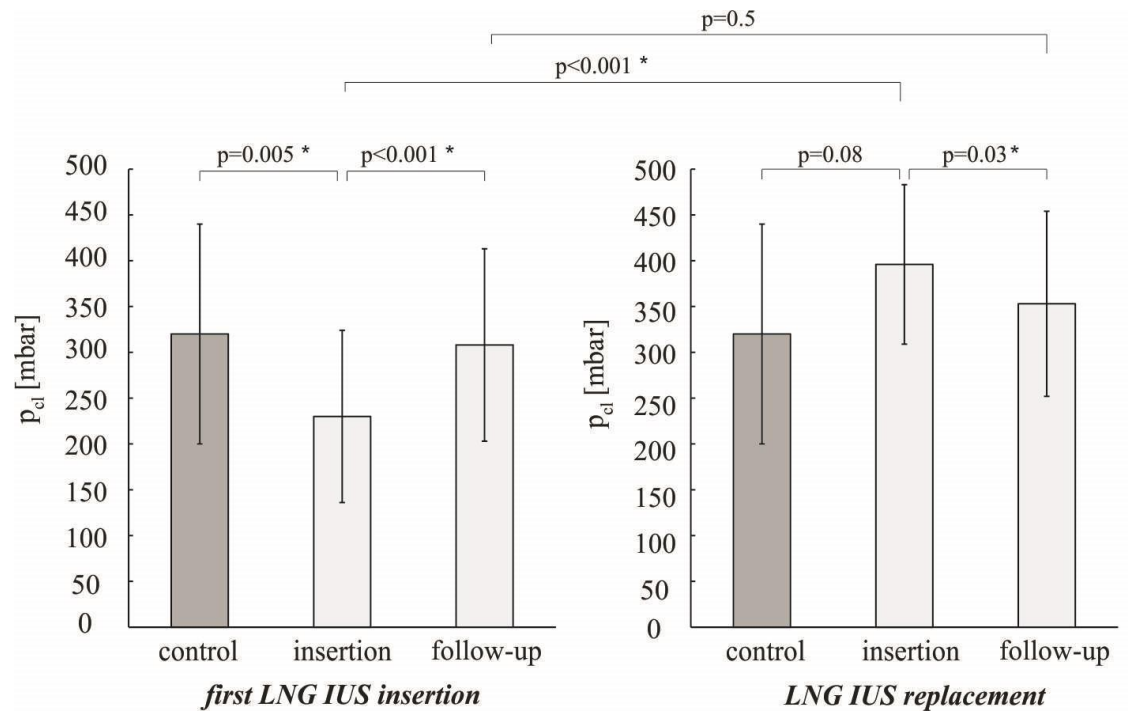


Fig. 2: Results of closure pressure p_{cl} (cervical stiffness) of the control group [25] and subjects at insertion and at follow up. Left: first LNG IUS insertions; Right: LNG IUS replacement. For all values, means and standard deviations and p-values are reported; significant results are indicated by * ($p < 0.05$).

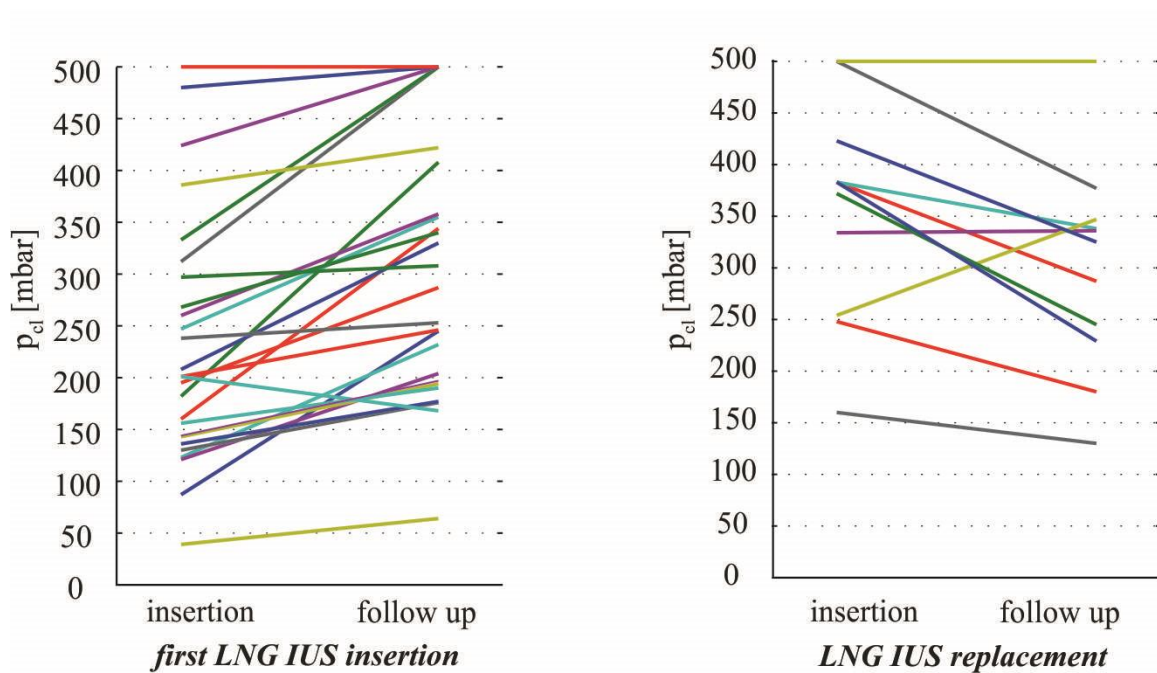


Figure 3: Pre and post-comparison of closure pressure p_{cl} (cervical stiffness) of each subject individually at insertion and at follow up. Left: first LNG IUS insertion; Right: LNG IUS replacement.